REMARKS

I. Status of the Claims

Claims 1-6, 8-24, and 26-41 are pending in this application.[1] Claims 7 and 25 were canceled in response to an Office Action dated May 9, 2005. Claims 30-38 have been withdrawn from consideration. Claims 1-6, 8-24, 26-29, and 39-41 have been rejected.[2] Claims 1, 8, 11, 12, 17, 19, and 40 have been amended as discussed further below.

Applicants acknowledge and appreciate the Examiner's withdrawal of

1. the rejection of claims 1-29 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement in the use of the terms "allyl" and "amidine";

2. the rejection of claims 1-29 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite in the use of the term "derivatives"; and

3. the rejection of claims 17-29 under 35 U.S.C. § 102(b) as being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as being obvious over EP 0 024 951 B1.

II. Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has maintained the rejection of claims 1-6, 8-24, and 26-29 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. (*Office Action* at p. 2.) Applicants respectfully traverse this rejection.

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[1] Applicants note that the Office Action Summary incorrectly indicates that claims 1-41 are pending in this application and respectfully request clarification of the record.

[2] Applicants note that the Office Action Summary incorrectly indicates that claims 1-29 and 39-41 are rejected and respectfully request clarification of the record.

A. The Examiner alleges that the specification does not enable treatment of Type I diabetes as claimed. (*Id.*) The Examiner admits that administering Gibberellins in combination with insulin is effective, but alleges that the specification does not provide evidence of effective treatment using combinations of Gibberellins and another substance as claimed. (*Id.* at p. 3.)

Applicants respectfully disagree. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent *coupled with information known in the art* without undue experimentation." M.P.E.P. § 2164.01 (emphasis added).

Applicants respectfully submit that the specification does enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation. In the specification, Example 5 demonstrates the effective treatment of Type I diabetes using Gibberellins in combination with a substance such as insulin. (*Declaration of Dr. Peter Jenkins* ("the Declaration"), filed September 9, 2005.) In fact, the Examiner admits that the evidence supports the efficacy of this combination for treating Type I diabetes. (*Office Action* at p. 3) The specification also refers to the known similarity between insulin's metabolic effects and substances such as IGF-1 and human growth factor. (*See*, e.g., *Specification* at p. 5, lines 13-31.) In fact, insulin fragment derivatives, IGF's and growth hormones are well known in the art to exhibit similar properties and metabolic effects as insulin. (*See*, e.g., "Antidiabetic Drugs." *The Year's Drug News, Therapeutic Targets* Barcelona: Prous Science, 1995, pp. 351-360.)

Thus, based on the disclosed efficacy of insulin in combination with Gibberellins, one of ordinary skill would have readily predicted that substituting insulin fragment

derivatives, IGF's and/or growth hormones for insulin in the administered combination with Gibberellins would be similarly effective in treating Type I diabetes. Given the protocols and guidance provided in the specification, e.g., Example 5, routine experimentation would allow the skilled artisan to assess the efficacy of administering Gibberellins with these insulin-like substances. Therefore, the present disclosure referring to treating Type I diabetes with a combination of Gibberellins and insulin enables the one of ordinary skill to perform the method as claimed without undue experimentation.

Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112.

B. The Examiner alleges that the specification does not enable the treatment of Type II diabetes as claimed. (*Office Action* at p. 3.) According to the Examiner, Example 5 does not describe treating Type II diabetes with Gibberellins alone. (*Id.*) The amount of insulin administered in Example 5 allegedly does not relate to the "amount of insulin present in the body" of a Type II diabetic. (*Id.*)

Applicants respectfully submit that Type II diabetes relates to an elevated blood glucose level and is not necessarily linked to any given insulin concentration. The World Health Organization describes Type II diabetics as having a "relative (rather than absolute) insulin deficiency." ("Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications", World Health Organization, Geneva 1999 at p. 23.) Specifically, Type II diabetics may have normal or even somewhat elevated levels of insulin. (*Id.* at p. 24.) Despite the seemingly adequate supply of insulin, however, their blood glucose level is abnormally high, indicating that this insulin concentration is not

sufficient to control their blood glucose level. (*Id.*) Such individuals are thus insulin resistant. (*Id.*) In other cases, insulin secretion is impaired, resulting in a lower than normal insulin concentration. (*Id.*) The insulin activity may be normal in these patients, but the insufficient insulin concentration gives rise to high blood glucose levels. (*Id.*) Type II diabetics can also exhibit both insulin resistance and impaired insulin secretion. (*Id.*) Therefore, Type II diabetics may have lower, similar or higher insulin concentrations compared to a non-diabetic, but in all these cases, their insulin level is insufficient to regulate their blood glucose concentration. Thus, contrary to the assertion of the Examiner, it is the elevated blood glucose level that is determinative of Type II diabetes, rather than any specific insulin concentration.

Example 5 of the present application describes the creation of a Type II diabetic model, whose blood glucose concentration was in the diabetic range despite its insulin concentration. (*See Declaration* at p. 7.) Male Wistar rats were induced with diabetes by administration of 60 mg/kg of streptozocin. (*Specification* at p. 22.) The resulting blood glucose level of ≥16 mM indicated that the rats were unequivocally diabetic. (*Declaration* at p. 4.) Streptozocin acts upon pancreatic β-cells and prevents endogenous production of insulin. (*Id.*) The skilled artisan would have appreciated that the amount of streptozocin adminstered would have induced Type I diabetes through the death of pancreatic β-cells. (*Id.* at p. 5.) Thus, Group Nos. 1-5 each had Type I diabetes at the outset of their treatment as described in the specification at pp. 22-23.

One of ordinary skill would appreciate that a blood glucose level of 4-6 mM is considered to be a normal level. (*Id.*) In Example 5, administration of 4 units/rat of insulin to Group No. 1 rats brought their blood glucose level to ranges that overlapped

with the 4-6 mM range, such that one of ordinary skill would have considered these rats to have achieved a normal blood glucose level. (*Id.* at p. 6.) In contrast, Group No. 2 rats, which were treated with only 2 units/rat of insulin, had blood glucose levels overlapping the ≥16 mM range, a range considered to be diabetic. (*Id.* at pp. 6-7.) Thus, 4 units/rat of insulin was sufficient to normalize the blood glucose levels of rats having Type I diabetes, but 2 units/rat of insulin was insufficient to bring their blood glucose level to a normal range. (*Id.* at p. 8.) The elevated blood glucose concentration, arising from an inadequate supply of insulin, caused the Group No. 2 rats to mimic the condition of a Type II diabetic. (*Id.* at p. 7.)

As in the Group No. 2 rats, administration of 2 units/rat insulin to the Group Nos. 3-5 rats served to create models of Type II diabetes. (*Id.* at p. 9.) However, the Group Nos. 3-5 rats were additionally treated with 5 mg/kg of Gibberellin A_3. (*Id.* at p. 7.) Where the Group No. 2 rats had a high blood glucose level, the Group Nos. 3-5 rats achieved blood glucose levels in the normal range of 4-6 mM. (*Id.*) The attainment of a normal blood glucose level thus arose from the administration of the Gibberellin A_3, as all of Group Nos. 2-5 rats were treated with 2 units/rat insulin. (*Id.* at p. 9.) Therefore, Example 5 fully enables the treatment of Type II diabetes through administration of Gibberellin A_3 alone. (*Id.*)

Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C § 112.

C. The Examiner alleges a lack of enablement in the use of the term "glycosidic." (*Office Action* at p. 3.) According to the Examiner, the term "glycoside" not only encompasses oligosaccharides and polysaccharides, but includes "any organic

chemical group derived from a sugar or starch molecule." (*Id.*) The Examiner alleges that an undue amount of experimentation would be required to identify active glycosidic compounds. (*Id.* at p. 3-4.)

Applicants disagree with the Examiner's interpretation of the term "glycosidic." In determining enablement, it is noted that the specification "need not teach, and preferably omits, what is well known in the art." (M.P.E.P. § 2164.01.) The term "glycoside" refers to a class of compounds well known in the art as of the present application's filing date. For example, Uvarov defines "glucoside" as a derivative of glucose where one hydrogen atom has been replaced by an organic radical. (Uvarov, E. B. et al. *A Dictionary of Science*, 4th Ed., Harmondsworth, England: Penguin Books, 1971, p. 169.) The term "glycoside" refers to such derivatives of all sugars, where "sugar" refers to any "sweet, soluble, *monosaccharide* or *disaccharide* carbohydrate." (*Id.* at pp. 169, 371) (emphasis added). Thus, the skilled artisan would appreciate that the term "glycoside" would relate to a mono- or disaccharide with a hydrogen atom replaced by an organic radical.

Glycosides have also been described as "sugar derivatives in which the hydroxyl group attached to carbon 1 is substituted by an alcoholic, phenolic or other group." (Sharp, D. W. A. *The Penguin Dictionary of Chemistry*, 5th Ed., Harmondsworth, England: Penguin Books, 1983, p. 193.) Sharp defines "sugars" as "carbohydrates, the majority of the natural sugars containing six or twelve carbon atoms in the molecule." (*Id.* at p. 376.) An introductory organic chemistry text refers to the term "glycosides" as cyclic acetals of monosaccharides, such as pyranosides (6-membered carbohydrate ring) and furanosides (5-membered carbohydrate ring). (Loudon, G.M. *Organic*

Chemistry, 3rd Ed. Redwood City, CA: Benjamin/Cummings Publishing Co., Inc., 1343-1346 (1995)). Common to all these descriptions of "glycoside" is that the term represents a substituent derived from a mono- or disaccharide.

Given these exemplary generic definitions, the skilled artisan would find further guidance as to the scope of "glycoside" from the context of the Gibberellins themselves. Several naturally occurring Gibberellins have monosaccharide glycosidic substituents, including glucopyranoside derivatives of Gibberellin A_3 and Gibberellin A_8, and glucosyl, hexa-Ac derivatives of Gibberellin A_8. (*See* Heilbron, I. M., Ed., *Dictionary of Organic Compounds*, 6th Ed., London: Chapman and Hall, 1996, pp. 2742-2743.) Thus, rather than blindly assume that "glycoside" must mean "any chemical group" derived from molecules spanning sugars to starches, Applicants respectfully submit that the skilled artisan would interpret the term "glycoside" based on well known definitions in the art and from the known naturally occurring Gibberellin glycosides. One of ordinary skill would readily appreciate the scope of "glycoside" in the present claims to reasonably encompass mono- and disaccharide glycosides, rather than derivatives of starch or other large polysaccharides. This understanding arises from knowledge well known in the art and thus does not require a teaching beyond that given in the specification. (*See* M.P.E.P. 2164.01.)

Given the knowledge in the field, the skilled artisan would be able to synthesize the claimed glycosyl ethers and esters in a routine manner. (*See*, e.g., *Loudon* at pp. 1346-1348.) Moreover, the specification at Examples 5-6 provides clear guidance on how to evaluate compounds of formula 1 for use in the claimed method, i.e., monitoring serum glucose levels. (*See Specification* at pp. 22-23.) Such guidance, coupled with

the knowledge in the art, have been shown to be sufficient evidence of enablement. *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988). Thus, the specification enables one of ordinary skill in the art to make and use the claimed invention through routine experimentation.

Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C § 112.

D. The Examiner alleges lack of enablement in the use of the terms "aryl," "arylalkyl," and "unsaturated or saturated ring." (*Office Action* at p. 4.) According to the Examiner, these terms are allegedly so broad that an undue amount of experimentation would be required to identify active compounds. (*Id.*) While Applicants disagree with the position of the Examiner, to advance prosecution, claims 1, 8, 11, 12, 17 and 19 have been amended to delete these terms, thereby rendering this rejection moot.

Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C § 112.

III. Rejection under 35 U.S.C. § 112, second paragraph

Claim 41 has been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for lack of antecedent basis for the term "the organic bases." (*Id.*)

Depending from method claim 11, claim 40 requires the pharmaceutically acceptable salt to be selected from a genus that includes "salts of ammonium or organic bases." Claim 41 depends from claim 40 and requires the organic bases to be selected from the genus recited therein. To clarify the antecedent basis of claim 41, Applicants

have amended claim 40 to recite "...ammonium or salts of organic bases." Applicants thus respectfully request withdrawal of this rejection.

IV. Rejections under 35 U.S.C. §§ 102 and 103

A. The Examiner has maintained the rejection of claims 17-24 and 26-29 under 35 U.S.C. § 102(b) as being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,580,857 ("Oden '857"), PCT Publication No. WO 96/20703 ("Wu") and PCT Publication No. WO 94/24260 ("Oden WO 94/24260"). (*Id.*)

The Examiner alleges that the cited references disclose compositions comprising Giberellins that do not require the presence of sugar. (*Id.* at p. 5.) According to the Examiner, these compositions therefore encompass Gibberellin compositions that require the absence of sugar. (*Id.*)

Currently amended independent claims 17 and 19 require an anti-diabetic agent comprising a Gibberellin of formula (1) in combination with substances selected from the group consisting of insulin, its fragment derivatives, IGFs, and growth factors, or combinations thereof. Support for this amendment can be found at least at p. 1, lines 20-26, of the specification. Accordingly, no new matter has been added.

Wu describes the use of Gibberellin compounds and corresponding pharmaceutical compositions for treating wounds, ulcers, and lesions, and for cultivation of skin cell lines. (*Wu* at p. 3.) However, Wu does not disclose, teach, or suggest an anti-diabetic agent requiring both the presently claimed Gibberellin of formula (1) and a substance selected from the group consisting of insulin, its fragment derivatives, IGFs, and growth factors, or combinations thereof. In fact, Wu provides no guidance to one of

ordinary skill to select a substance such as insulin for use in its compositions. Thus, Wu neither anticipates nor renders obvious the present claims.

Similarly, Oden '857 and Oden WO 94/24260 do not teach anti-diabetic uses of Gibberellin compounds. Namely, Oden '857 discloses the use of Gibberellin compounds for the treatment of prostatitis and psoriasis. (*Oden '857* at col. 2, lines 31-34.) Oden WO 94/24260 discloses a composition "containing one or more gibberellins with activity against androgenic alopecia." (*Oden WO 94/24260* at p. 5.)

As discussed above, claims 17 and 19 have been amended to require a substance selected from the group consisting of insulin, its fragment derivatives, IGFs, and growth factors, or combinations thereof. Oden '857 and Oden WO 94/24260 do not disclose, teach, or suggest an anti-diabetic agent requiring any of these substances. Therefore, neither of these references anticipate or render obvious the present claims. Thus, claims 17-29 are patentable over Oden '857 and Oden WO 94/24260.

Accordingly, Applicants respectfully request withdrawal of these rejections.

B. The Examiner has maintained the rejection of claims 1-6, 8-24 and 26-29 under 35 U.S.C. § 102(b) as being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as being obvious over Davis et al., *Journal of the American Podiatric Medical Association* (1989) 79:1, 24-26 ("Davis"). (*Office Action* at p. 5.) Applicants respectfully traverse this rejection.

The Examiner alleges that the claimed treatment of diabetes is inherent in Davis' administering a Gibberellin compound to treat inflammation in diabetic mice. (*Id.*) Applicants disagree for at least the following reasons.

"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'" M.P.E.P. § 2112 (quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teaching of the applied prior art." *Id.* (quoting *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)). Applicants respectfully submit that the Examiner has failed to do so.

In contrast to the presently claimed methods, Davis teaches a method of treating inflammation using a composition containing Gibberellin. (*Davis* at p. 24.) Davis used diabetic mice in its study "because of their poor healing and anti-inflammatory capabilities." (*Id.*) Davis created a site of inflammation on the mice by subcutaneous injection of a 2% gelatin solution. (*Id.* at p. 25.) After administration of a Gibberellin solution, the mice were killed three hours later for analysis of inflammation activity. (*Id.*) Davis evaluated the effect of Gibberellin on inflammation by measuring the reduction of polymorphonuclear leukocyte cells (PMNs) at the site of inflammation. (*Id.*)

Davis does not describe, teach, or suggest the treatment of diabetes itself. As discussed above, treatment of diabetes involves bringing a patient's elevated blood glucose level to within the normal range of 4-6 mM. (*See Declaration* at p. 5.) Yet, one of ordinary skill in the art would appreciate that no direct correlation exists between treating inflammation and lowering blood glucose concentration. For example, Shurtz-Swirski attributes the inflammation associated with Type II diabetics to oxidant release

by PMNs. *Diabetes Care*, 24:104-110 (2001). Shurtz-Swirski demonstrated that oxidant release by diabetic human PMNs is significantly higher when compared to the PMNs in control subjects. (*Id.* at p. 104.) However, no correlation between the rate of PMN oxidant release and the same individual's blood glucose level was observed. (*Id.* at pp. 106-107.)

Thus, Davis' observed decrease in PMN cells in treating inflammation is likely accompanied by a decrease in the rate of oxidant release. However, a concomitant reduction in blood glucose levels does not "necessarily flow" from a decrease in the PMN oxidant release. As Davis provides no explicit or implicit disclosure that its method did effect a decrease in the subjects' blood glucose levels, Davis fails to provide an inherent disclosure of the presently claimed method, and thus fails to anticipate the present claims. In addition, Davis does not teach or suggest a method of treating diabetes and its complications and associated conditions, as claimed. Therefore, the Examiner has failed to establish a prima facie case of obviousness over the claimed method.

Finally, Davis does not disclose, teach, or suggest an anti-diabetic agent as recited in claims 17-24 and 26-29 for the same reasons discussed above for Wu.

Accordingly, Applicants respectfully request withdrawal of this rejection.

V. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: February 6, 2006

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